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# Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States)

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## Abstract

*Background*: Ethylene oxide (ETO) is a sterilant gas considered to be a human carcinogen, due primarily to excess hematopoietic cancer in exposed cohorts. ETO causes mammary tumors in mice, and has been associated with breast cancer incidence in one small epidemiologic study.
*Methods*: We have studied breast cancer incidence in a cohort of 7576 women employed for at least one year and exposed for an average 10.7 years while working in commercial sterilization facilities. Breast cancer incidence (n = 319) was ascertained *via* interview, death certificates, cancer registries, and medical records. Interviews were obtained for 68% of the cohort.
*Results*: The standardized incidence ratio (SIR) for incident breast cancer in the whole cohort using external referent rates (SEER) was 0.87 (0.77–0.97). The SIR for those in the top quintile of cumulative exposure, with a 15 year lag, was 1.27 (0.94–1.69), with a positive trend of increasing SIR with increasing exposure ($p = 0.002$). SIRs are underestimated because breast cancer incidence in the whole cohort was under-ascertained, due to incomplete response and lack of complete coverage by state cancer registries. In internal nested case–control analyses of those with interviews (complete cancer ascertainment), controlling for reproductive risk factors, a positive exposure–response was found with the log of cumulative exposure with a 15-year lag ($p = 0.0005$). The odds ratio by quintile of cumulative exposure were 1.00 (0 exposure due to 15 year lag), 1.06, 0.99, 1.24, 1.42, and 1.87.
*Conclusions*: Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure–response trends and possible biases due to non-response and incomplete cancer ascertainment.

## Introduction

Ethylene oxide (ETO) is widely used as a sterilant gas and an industrial chemical. NIOSH has estimated that approximately 270,000 people were exposed in the US in the 1980s, principally in hospitals (96,000) and commercial sterilization (21,000) [1]. Exposure levels to ETO in the US have decreased greatly since the early 1980s when a one ppm standard was instituted, based on early findings of leukemia in animals and humans.

ETO is a direct-alkylating agent which causes increased chromosomal aberrations and sister-chromatid exchange [2]. Inhaled ETO is quickly absorbed in the lungs and distributed rapidly throughout all tissues; it forms dose-related hemoglobin adducts in people and rodents, and dose-related DNA adducts in rodents [2]. The International Agency for Research on Cancer (IARC) has determined that ETO is a definite (Group 1) human carcinogen, based on limited evidence from epidemiologic studies showing increased hematopoietic cancer, supported by positive human cytogenetic evidence, and on sufficient evidence from animal studies for hematopoietic and other cancers [2].

Besides hematopoetic cancer, more recently there has been concern that ETO might also be linked to breast cancer, based on limited evidence. Norman *et al.* [3] found a statistically significant twofold increase in breast cancer incidence based on 12 observed cases among

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women exposed at a commercial sterilization plant. A cluster of breast cancers was observed among Hungarian hospital workers exposed to ETO [4]. Furthermore, animal data indicated that ETO caused mammary tumors in mice [2], although not in rats. However, two other small incidence studies (together based on fewer than 10 cases) did not show an excess of breast cancer [5, 6]. Two mortality studies, one small [7] (four breast cancer deaths) and one large [8] (a NIOSH study of 10,000 women, 42 breast cancer deaths) also failed to show an excess. To study this issue further we have conducted a breast cancer incidence study of 7576 women from the NIOSH cohort employed for at least one year.

## Methods

### *Cohort definition*

This study of breast cancer incidence was based on the women in a US cohort of 18,000 men and women exposed for at least three months to ETO, from the 1940s to the 1980s. The original cohort was assembled by NIOSH in the mid-1980s, and has been previously studied for mortality [8]. Cohort members worked at 14 plants in 11 states.

### *Interviews*

We sought cancer incidence information for 7576 women (76% of women in the original cohort) who had worked for at least one year. The restriction to those with at least one year employment was motivated by cost considerations and the greater difficulty of locating women with short term employment. Follow-up for breast cancer in the present study began no earlier than one year after the beginning of employment, or after three months of exposure, whichever date was later.

We sent a written questionnaire to all women, or their next-of-kin (18% of the cohort had died), for whom we could find valid addresses. After two mailings and a reminder postcard, we called non-respondents, at varying times of day and days of the week. When possible, the interview was then conducted by phone. Addresses and telephone numbers were identified using a variety of strategies including the Internal Revenue Service, the US Postal Service, motor vehicle registration, credit bureaus, and telephone number look-up services. The interview asked about ethnicity, education, height, weight, longest job, menstrual and reproductive history (including number and dates of pregnancies, and pregnancy outcomes), use of hormones, smoking history, alcohol history, diet, and cancer history (with extra detail on breast cancer).

### *Breast cancer ascertainment*

Breast cancer cases were identified by the interview. In addition, ascertainment was also conducted *via* death certificates and cancer registries. Cancer registries were available in nine of the 11 states in which plants were located, but often for limited periods of time (Texas 1992, 1995–1997, Georgia 1975–1998 for Atlanta area, 1995–1998 for entire state, Kentucky 1991–1998, Maryland 1992–1998, Florida 1981–1998, New Jersey 1979–1998, Connecticut 1935–1998, South Carolina 1996–1998, New York 1976–1998). We matched women who had worked in a given state or contiguous state against cancer registries for that state; for Florida we matched the entire cohort under the assumption that women from any state may have retired there.

Medical record confirmation was sought for all cancers reported on interview. We also sought medical records for all decedents who died of cancer. However, cases identified by self-report or death certificates, for whom no medical record was obtained, were included in the analysis.

### *Follow-up methods and definition of end of follow-up*

Mortality follow-up was extended beyond the previous 12/31/1987 until 12/31/1998, *via* Social Security, the Internal Revenue Service, and the National Death Index (NDI). Causes of death were obtained from NDI. Vital status for deaths prior to the existence of NDI (prior to 1979) were identified by Social Security and Internal Revenue Service records, and causes of death were obtained *via* death certificates obtained from states.

Follow-up for breast cancer incidence was likewise terminated as of 12/31/1998. Dates of diagnosis were obtained from self-report, medical record, cancer registry, or next-of-kin. In case of multiple dates the earliest and/or the date considered most valid was used. For breast cancer decedents for whom no other source was available, date of death was used as date of diagnosis. If a women or her next-of-kin reported breast cancer, but this report was specifically contradicted by medical record or cancer registry data, this woman was not included in the analysis as a case ($n = 6$). If a women or their next-of-kin did not report breast cancer on interview but breast cancer was found in the medical record or cancer registry record, then these women were included as a case ($n = 25$).

### *Exposure estimates*

Estimated exposures over time for this cohort had been developed previously, based on a large number of

measurements coupled with data on historical process changes [9]. Exposure estimates covered all years during which employees were exposed, and were derived from a model which explained 85% of the variance of the observed sampling data. One small plant in the original cohort (19 women with more than one year employment) lacked exposure estimates, and was excluded from the present study.

Work history data had been gathered originally in the mid-1980s. Some plants in the study continued using ETO after this point, and for them we gathered additional information on the date-last-employed for those who had been employed at the time work history was collected (25% of the cohort). Work history for these women was extended until the date-last-employed at the plant in question; it was assumed that they did not change jobs and that the level of ETO exposure remained the same as in their last job in the mid-1980s. Cumulative exposure calculated with and without the extended work histories differed little because exposures were very low by the mid-1980s.

*Analyses using the full cohort and an external comparison*

Breast cancer incidence was analyzed in the entire cohort (n = 7576) *versus* an external non-exposed population (the SEER population). Ascertainment of breast cancer in the entire cohort was known to be incomplete, because some women did not have interviews and did not live in states with cancer registries. It was not possible to estimate the degree of under-ascertainment.

Life-table analyses of the entire cohort were done using the NIOSH Life-Table Analysis system [10] (www.cdc.gov/niosh/ltdoc.html), using referent rates developed from SEER (Surveillance, Epidemiology, and End Results) data for the period 1970–1999, for invasive female breast cancer (ICD 9th revision code 174) and *in situ* breast cancer (ICD 9th revision code 233.0). The SEER data represent approximately 10% of the US population.

Analyses using SEER referent rates produced standardized incidence ratios (SIRs) by categories of the cumulative exposure (ETO ppm-days), stratified by age (five year categories), calendar time (five year categories), and race/ethnicity (white and non-white). Follow-up time began in 1970 when the SEER rates begin, or one year after first employment, or at the date of first exposure plus 90 days (a requirement for cohort entry in the original study), whichever was later. The restriction of follow-up to the period post-1970 was presumed to have little effect on results because it eliminated only three percent of the breast cancer cases and seven percent of the person-time which would have been available without this restriction. Follow-up continued until date of death (or date of diagnosis, for breast cancer cases), end-of-study (12/31/1998), or date-last-observed for those lost-to-followup, whichever was earliest.

Categorical analyses by cumulative exposure (ETO ppm-days) using data from the life-table analyses were done by quintiles, based on the cases = cumulative exposure. Analyses with a 15 year lag were also conducted; a 15 year lag was chosen based on having the best fit to the data in internal regression analyses (see below). A 15 year lag discounts all exposure occurring with the last 15 years, and in some instances results in a case having no exposure ("lagged out"). Quintiles in lagged analyses were formed based on the cumulative exposure of all cases not "lagged out".

Trend tests for trends in SIRs with cumulative exposure (in which the lowest exposed group was the referent) were done *via* Poisson regression (SAS GENMOD [11]). For analyses using the log of cumulative exposure with a lag, a cumulative exposure of one ppm-day was added to everyone's cumulative exposure to avoid taking the logarithm of 0.

Breast cancer-*in situ* was reported for six percent of the cases (20/319). *In situ* and invasive cancer cases were analyzed separately when using external referent rates (SEER rates), and results then combined. *In situ* cases were likewise included in internal Cox regression analysis. Results did not differ greatly with the inclusion or exclusion of *in situ* cases.

*Analyses using either the full cohort or those with interviews, with internal comparisons*

Internal exposure–response analyses using a nested case–control design were conducted using Cox regression for the entire cohort (n = 7576) and for the sub-cohort with interviews (n = 5139). Analyses were done using the SAS PHREG procedure [11]. Breast cancer ascertainment in the sub-cohort with interviews was considered complete, and analyses based on interviews were able to include variables for reproductive risk factors.

In these analyses the time variable was age (effectively matching on age), and risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without breast cancer to at least the age of the index case; 100 controls has been shown to be sufficient to obtain a good approximation of the rate ratio obtained using all possible controls (the full risk set), with approximately the same precision [12]. Cases and controls were matched on race (white/non-white).

Exposure in these analyses was truncated if it extended beyond the age of the case failure.

For the analysis of the sub-cohort with interviews, we considered variables thought a priori to be associated with breast cancer and hence to be possible confounders, including body mass index, breast cancer in a first-degree relative, parity, age at menopause, age at menarche, socioeconomic status, and diet. Of these only parity and breast cancer in a first-degree relative proved to be important predictors of breast cancer, and only these were included in final models. Menopausal status was considered a possible effect modifier and analyzed as such.

Exposure–response analyses in Cox regression focused on cumulative exposure or the log of cumulative exposure, with or without a lag for exposure. The log of cumulative exposure tends to reduce the influence of very high exposures in skewed exposure distributions, and sometimes improves fit over untransformed cumulative exposure. We also tried models using peak exposure (highest one time exposure) or average exposure (cumulative exposure divided by duration of exposure).

To investigate further the shape of the exposure-response curve, we conducted a restricted cubic-spline analysis with six knots. This analysis fitted a cubic exposure–response curve between knots, while fitting a linear model before and after the first and last knots [13].

## Results

Completed interviews were obtained for 5139 (68%) of the 7576 women in the cohort. The principal reason for no interview was inability to locate the respondent (22%), rather than refusal (7%), or failure to respond after repeated attempts (3%). Reasons for not locating women or their next-of-kin included a lack of good addresses for tracing next-of-kin of deceased subjects (we had no SSNs, the best identifier, for next-of-kin), and the lack of recent or valid addresses for live subjects provided from IRS or credit bureaus (often several years out of date).

Of the entire cohort, the average duration of exposure was 10.7 years (s.d. 9.2), and 1327 (18%) had died. Interviews were available (from next-of-kin) for 55% of decedents, compared to 71% among the living. Non-respondents had a median year of birth of 1937, and had a median cumulative dose to ETO of 8.0 ppm-years; the corresponding figures for respondents were 1938 and 8.6 ppm-years. While the level of non-response (32%) is of concern, we attempted to determine breast cancer incidence for the entire cohort *via* sources other than the interview, and a number of analyses were based on the entire cohort. Furthermore, results for the entire cohort (incomplete ascertainment) were similar to the results for the sub-cohort with interviews (complete ascertainment).

*Table 1.* Source of breast cancer cases (n = 319)

| Source (more than one source per case possible) | Number of cases identified by source (%) |
|---|---|
| Death certificates | 95 (30) |
| Cancer registries | 182 (57) |
| Medical record[a] | 144 (45) |
| Interview (live)[b] | 147 (46) |
| Interview (dead)[b] | 60 (19) |

[a] Eighty-five percent with histopathology confirmation in the record.

[b] Two hundred and thirty three breast cancer cases or their next-of-kin had interviews. Medical record or cancer registry confirming their breast cancer was found for 189 of these (81%). Twenty-five interviews did not indicate that the respondent or the decedent (for next of kin interviews) had breast cancer on the interview (some next-of-kin did not answer this question), but breast cancer was found *via* medical record or cancer registry data. Six other women or their next-of-kin reported breast cancer on interview, but these reports were contradicted by medical record or cancer registry record; these women were therefore not considered cases.

There were 319 incident breast cancers identified among the cohort through the end of 1998, who were eligible for the study (diagnosed after one year after first employment and 90 days exposure). Table 1 provides information regarding the source of these 319 cases. Thirty-nine percent (124/319) of these cases had died by the end of 1998. Six percent were carcinoma-*in situ* cases (n = 20). Seventy-three percent (n = 233) had interview data. Although breast cancer was ascertained for 30% of cases from death certificates, this was the only source for only 14% of cases; therefore for only 14% of cases did we use date of death as date of diagnosis.

Table 2 provides some descriptive information on cases and non-cases from among those who had

*Table 2.* Description of cases and non-cases with interview data[a]

| Variable | Cases (n = 233) | Non-cases (n = 4906) |
|---|---|---|
| % Nulliparous | 15.0% | 11.6% |
| % With first-degree relative with breast cancer | 16.3% | 10.3% |
| % Pre-menopausal at diagnosis | 14.4% | n.a. |
| Mean year of birth | 1932 (s.d. 11.3) | 1938 (s.d. 12.6) |
| Mean number of children | 2.29 (s.d. 3.52) | 2.36 (s.d. 3.34) |
| Mean BMI age 20 | 20.8 (1.6) | 21.0 (1.6) |
| Median cumulative exposure | 14.0 ppm-years | 8.4 ppm-years |
| Means years exposed | 13.0 (s.d. 9.2) | 10.9 (s.d. 9.4) |

[a] Based on those with complete interview data for parity and breast cancer in first degree relatives. Somewhat fewer subjects had complete data for menopausal status and BMI.

*Table 3.* Rate ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), life table and Poisson regression analyses of entire cohort (n = 7576)

| | 0 (lagged out) | <647 | 647–2026 | 2026–4919 | 4919–14,620 | >14,620 | Combined exposed | Test for trend, for cum. exp. or log cum. exp.[b] |
|---|---|---|---|---|---|---|---|---|
| 15 year lag | | | | | | | | |
| External referent[a] | 0.88 (0.67–1.04) | 0.77 (0.56–1.03) | 0.77 (0.56–1.03) | 0.94 (0.69–1.25) | 0.83 (0.61–1.11) | 1.27 (0.94–1.69) | 0.89 (0.78–1.01) | Linear, $p = 0.002$ log $p = 0.05$ |
| Observed cases[c] | 81 | 45 | 46 | 46 | 45 | 48 | 230 | |
| | | <855 | 855–2596 | 2596–6343 | 6343–16,447 | >16,447 | | |
| No lag | | | | | | | | |
| External referent[a] | n.a. | 0.74 (0.57–0.97) | 0.81 (0.62–1.04) | 0.92 (0.70–1.18) | 0.91 (0.70–1.17) | 1.02 (0.79–1.30) | 0.87 (0.77–0.97) | Linear, $p = 0.16$ log $p = 0.08$ |
| Observed cases | | 60 | 62 | 63 | 62 | 64 | 311 | |

[a] External referent is US population, SEER cancer incidence rates, 1970–1998, indirectly SIRs stratified for age (5 year categories), ethnicity (white/non-white), and calendar time (5 year categories).
[b] Test for trend (internal referent) calculated *via* Poisson regression, adjusted for age (5 year categories), calendar time (5 year categories), ethnicity (white/non-white).
[c] Three hundred and eleven (of 319) cases were included; eight cases were diagnosed before 1970 when SEER rates became available.

interview data. Cases were older, had fewer children, and were more likely to have had a first-degree relative with breast cancer.

Table 3 provides the results of the life-table analysis of breast cancer incidence for the whole cohort. Overall the cohort had a SIR of 0.87 (0.94 when *in situ* cases were excluded). However, the true number of breast cancers was under-ascertained, so that the SIR based on external SEER comparison rates is underestimated. Regarding exposure-response trends, for the data with a 15 year lag there is a positive trend of higher SIRs ratios with higher cumulative exposure ($p = 0.002$ for cumulative exposure, $p = 0.05$ using the log of cumulative exposure). For the unlagged data, the trend with cumulative exposure was less marked ($p = 0.16$ for cumulative exposure, $p = 0.08$ using the log of exposure).

Results of internal analyses using all cases (319 cases, including 20 *in situ* cases) are shown in Table 4 (adjusted only for year of birth and age). In categorical analyses using a 15-year lag, the top quintile had an odds ratio of 1.74 (95% CI: 1.16–2.65). The best fitting model with exposure as a continuous variable was one using the log of cumulative exposure, lagged 15 years ($p = 0.05$). However, a model using duration of exposure (with a 15 year lag) fit slightly better than the model using cumulative exposure to ETO. Duration of exposure and cumulative exposure are correlated (Spearman correlation coefficient 0.36). Models using peak or average exposure did not fit as well and are not shown.

Internal analysis for those with interviews (n = 5139, 233 cases) are shown in Table 5. These models are adjusted for parity (any children *versus* none), breast cancer in a first-degree relative, and year of birth (quartiles). The results in Table 5 are concordant with Table 4, although exposure response coefficients were slightly higher and the models using the log of cumulative exposure (lagged 15 years) and untransformed cumulative exposure (lagged 15 years) fit about equally well. Duration of exposure (with a 15 year lag) again fit slightly better than cumulative exposure to ETO in a model using continuous variables.

Of the 233 cases with interviews, menopausal status was unknown or missing for 38, was pre-menopausal for 28, and was post-menopausal for 167. Using a model with log cumulative exposure (15 year lag), year of birth, breast cancer in first degree relatives, and parity, the exposure–response coefficient was 0.051 (s.e. 0.024, $p = 0.04$) for post-menopausal women, and 0.036 (s.e. 0.041, $p = 0.34$) for pre-menopausal women.

Figure 1 shows the exposure–response curves for the full cohort (n = 7576, 319 cases) based on internal analyses (units are ppm-days). The figure shows the

*Table 4.* Odds ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), Cox regression analyses[a] of entire cohort (n = 7576, 319 cases)

| Exposure variable | Coefficient, (s.d.), *p*-value | Odds ratios by category[b] |
|---|---|---|
| Categorical, cumulative exposure lagged 15 years (quintiles) | n.a. | 1.00 (lagged out), 1.07 (0.72–1.59), 1.00 (0.67–1.50), 1.24 (0.85–1.90), 1.17 (0.78–1.78), 1.74 (1.16–2.65) |
| Categorical, cumulative exposure, no lag (quintiles) | n.a. | 1.00, 0.98 (0.69–1.38), 1.07 (0.76–1.51), 1.13 (0.80–1.59), 1.16 (0.82–1.65) |
| Categorical, duration of exposure, lagged 15 years (quintiles) | n.a. | 1.00, 0.98 (0.66–1.45), 1.15 (0.77–1.73), 1.37 (0.91–2.04), 1.10 (0.73–1.67), 1.91 (1.22–2.15) |
| Continuous, log cumulative exposure lagged 15 years | 0.037 (0.019), $p = 0.05$ | n.a. |
| Continuous, log cumulative exposure | 0.049 (0.034), $p = 0.14$ | n.a. |
| Continuous, cumulative exposure, lagged 15 years | 0.0000054 (0.0000035), $p = 0.12$ | n.a. |
| Continuous, cumulative exposure | 0.0000013 (0.0000030), $p = 0.66$ | n.a. |
| Continuous, duration exposure, lagged 15 years | 0.028 (0.02), $p = 0.02$ | n.a. |
| Continuous, duration exposure | 0.012 (0.008), $p = 0.17$ | n.a. |

[a] Odds ratios calculated *via* Cox regression, cases and controls matched on age, ethnicity (white/non-white), all models include cumulative exposure and categorical variable for year of birth (quartiles).
[b] Categories for cumulative exposure are the same as Table 3.

*Table 5.* Odds ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), Cox regression analyses[a] of cohort with interviews (n = 5139, 233 cases)

| Exposure variable | Coefficient, (s.e.), *p*-value | Odds ratios by category[b] |
|---|---|---|
| Categorical, cumulative exposure lagged 15 years (quintiles) | n.a. | 1.00 (lagged out), 1.06 (0.66–1.71), 0.99 (0.61–1.60), 1.24 (0.76–2.00), 1.42 (0.88–2.29), 1.87 (1.12–3.10) |
| Categorical, cumulative exposure, no lag (quintiles) | n.a. | 1.00, 1.25 (0.83–1.88), 1.19 (0.78–1.83), 1.52 (1.00–2.29), 1.41 (0.92–2.16) |
| Categorical, duration of exposure, lagged 15 years (quintiles) | n.a. | 1.00, 1.00 (0.63–1.60), 1.18 (0.73–1.90), 1.39 (0.86–2.25), 1.11 (0.67–1.82), 2.32 (1.37–3.94) |
| Continuous, log cumulative exposure lagged 15 years | 0.050 (0.023), $p = 0.03$ | n.a. |
| Continuous, log cumulative exposure | 0.092 (0.041), $p = 0.02$ | n.a. |
| Continuous, cumulative exposure, lagged 15 years | 0.0000095 (0.0000041), $p = 0.02$ | n.a. |
| Continuous, cumulative exposure | 0.0000059 (0.0000035), $p = 0.10$ | n.a. |
| Continuous, duration exposure, lagged 15 years | 0.039 (0.014), $p = 0.006$ | n.a. |
| Continuous, duration exposure | 0.019 (0.010), $p = 0.07$ | n.a. |

[a] Odds ratios calculated *via* Cox regression, cases and controls matched on age, ethnicity (white/non-white), all models include cumulative exposure and categorical variables for year of birth (quartiles), breast cancer in first-degree relative, and parity.
[b] Categories for cumulative exposure are the same as Table 3.

categorical data, and three different models (cumulative exposure, log of cumulative exposure, and the spline curve). It is visually apparent that the log of cumulative exposure fits the categorical data and corresponds well with the spline curve.

While biological considerations do not generally favor the possibility of thresholds for carcinogens (exposure levels below which there is no risk), we also tested a threshold model. The best fitting threshold model (6.2 log ppm-days with a 15 year lag, equivalent to 1.3 years of exposure under the current standard of 1 ppm) was not a statistical significant improvement over the non-threshold model (model likelihood 25.9 *versus* 24.0, respectively).

The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure. Further categorical analyses using deciles of cumulative exposure (with a 15 year

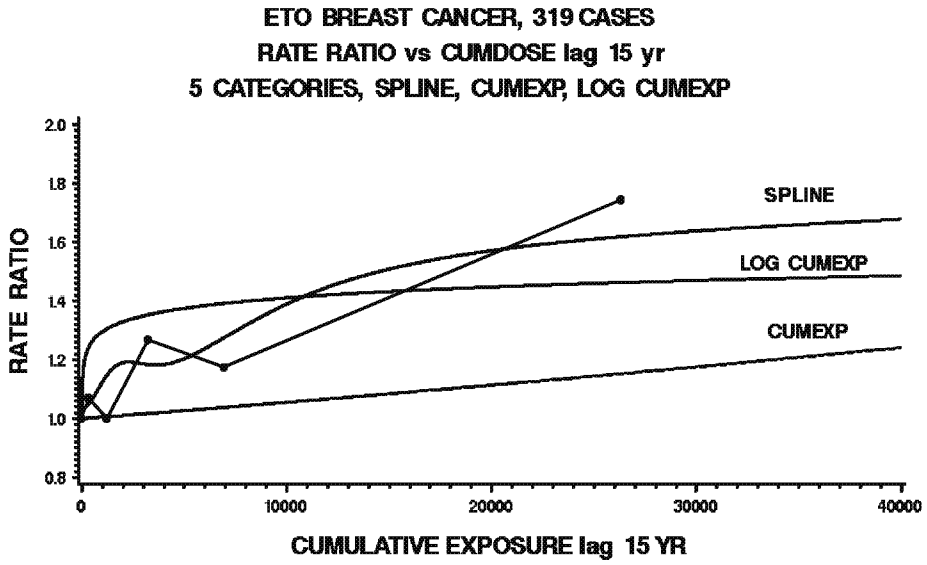


*Fig. 1.* Exposure–response curves, internal analysis.

lag) rather than quintiles revealed that the 8th decile had no excess risk (odds ratios by decile *versus* those lagged out, 0.88, 1.35, 1.00, 1.00, 1.33, 1.22, 1.40, 1.03, 1.68, 1.82).

There were at least two possible biases which might have biased our results towards higher breast cancer rates among the more highly exposed. First, women with longer cumulative exposure tend to be those who worked longer (Spearman correlation, 0.36), and workers with longer employment may have had more screening *via* mammography because they had good medical surveillance and insurance coverage (although women who left employment with a study company may well have found other employment elsewhere with equally good medical benefits). We had some limited data on mammography for live respondents. After excluding women with breast tumors lumps, or cysts, who would have had more mammograms subsequent to such problems, and after controlling for age, we did not find a strong association between cumulative exposure (in quintiles) and number of mammograms (0, 1–5, 6–10, 10+) *via* contingency table analysis ($p = 0.25$). Furthermore the Spearman correlation coefficient between cumulative dose and number of mammograms (categories scored 0, 1, 2, 3) was low, only 0.08. Thirty-nine percent of women in the highest exposure quintile had more than five mammograms, *versus* 30% of women in the low exposure quintile. Restriction of the data to those with at least five years after exposure, when this possible bias might be expected to diminish, did not result in decreased exposure-response trends. All in all, there was no strong evidence (based on limited data) that this bias was important.

A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and hence greater cumulative exposure. Unfortunately, we did not have residential history, limiting our ability to explore this possibility. We did, however, compare the cumulative exposure of women whose cancer was ascertained *via* cancer registry (n = 182) and women whose cancer was ascertained only *via* other records (n = 137). Cumulative exposure was greater in the cases ascertained *via* cancer registry, but this difference was not statistically significant ($p = 0.13$). Again, we did not consider this to be strong evidence, based on limited data, for this potential bias.

## Discussion

Our data do not indicate any overall excess of breast cancer incidence among the cohort as a whole compared to the US population. However, cancer incidence was under-ascertained because of inability to locate some cohort members and because of incomplete coverage of the cohort by state cancer registries. We were able to contact only 68% of our cohort directly, and only about 50% of the cohort worked in states with cancer registries covering many years. It is not possible to accurately estimate the degree of under-ascertainment. Even with the under-ascertainment, however, we did find that those in the upper quintile of cumulative exposure, with

a 15 year lag, had a 27% increase in breast cancer incidence compared to the SEER non-exposed population (34% after excluding *in situ* cases).

Because of the issue of under-ascertainment, we have emphasized internal exposure-response analyses in our study rather than the use of external referent population. Exposure-response data do suggest an increased risk of incident breast cancer for those with higher cumulative exposures to ETO. This is especially apparent for exposures occurring 15 or more years before breast cancer occurrence.

Those in the top quintile of cumulative exposure, with a 15 year lag, showed an odds ratio of 1.74 (95% CI: 1.16–2.65) in internal analyses based on all 319 cases compared with the lagged out group. The odds ratio was 1.87 (95% CI: 1.12–3.10) in a similar analysis based on 233 cases with interview data, which controlled for parity and breast cancer in first degree relatives. Less excess risk for the upper quintile was seen without the lag. However, use of a lag is consistent with a necessary latency period for solid tumors. The best fitting models for the exposure-response trend used a lag of 15 years and a log transformation of cumulative exposure, and showed statistically significant positive trends. The log transformation implies that rate ratios tend to flatten out or plateau at very high exposures, rather than increasing in a linear fashion. This phenomenon has been seen in other occupational carcinogens such as dioxin, silica, and diesel fumes [14–16], and has been discussed in detail in relation to arsenic [17].

There are two factors which tend to weaken the case for a causal relationship suggested by the positive exposure–response findings. One is that similar effects were seen using duration of exposure rather than cumulative exposure. This raises the possibility that some other factor related to duration of exposure could be associated with increased breast cancer risk, rather than cumulative exposure to ETO. Secondly, the increase in risk did not increase consistently (monotonically) with increasing cumulative exposure, especially in categorical analyses with 10 categories.

On the other hand, there are counter-arguments to these weaknesses. Since duration of exposure is one component of cumulative exposure, the two are necessarily correlated (Spearman correlation coefficient 0.36), and it is not unexpected for exposure–response trends to exist for both measures. There are many uncertainties in estimating past exposures based on limited actual measurements. We did not have measured exposure levels for each person in our study, but instead estimated exposure levels over time based on existing measurement for different job categories. The method undoubtably led to errors in estimating exposure for individuals. Errors in estimating exposure can lead to similar imprecision in estimating exposure-response trends. However, imperfect exposure estimation is typical of most retrospective epidemiologic studies. The exposure estimation for this cohort was based on a relatively large number of existing samples and is probably one of the better examples in the literature of retrospective exposure assessment. Our model predictions out-performed the best guesses of a panel of industrial hygienists assembled to evaluate our exposure prediction model [9].

Regarding the inconsistency of the exposure-response trend, it is not uncommon for such trends to exhibit fluctuations, some of which may be due to random variation, others of which might occur due to imprecision in estimating exposure.

There was evidence supporting a positive exposure-response from mortality data for women through 1998 for this same cohort [18]. The overall breast cancer standardized mortality ratio (SMR) for the 9885 women in the original NIOSH cohort (without the one year employment restriction) was unremarkable (SMR 0.99, 102 deaths). Exposure–response analyses indicated the highest exposure quartile had an SMR of 1.27 based on 26 deaths. When a 20-year lag was applied, the highest exposure quartile had an SMR of 2.07 (95% CI: 1.10–3.54, based on 13 deaths).

In summary, our data do suggest that ETO exposure is associated with increased incidence of breast cancer. However, there are some inconsistencies in the exposure-response data, and there are possible biases due to patterns of non-response and cancer ascertainment which introduce additional uncertainties in the findings. Exposure levels to ETO in the US have decreased greatly since the early 1980s when a one ppm standard was instituted.

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